# Neuropsychological Changes Associated with Normal and Pathological Aging

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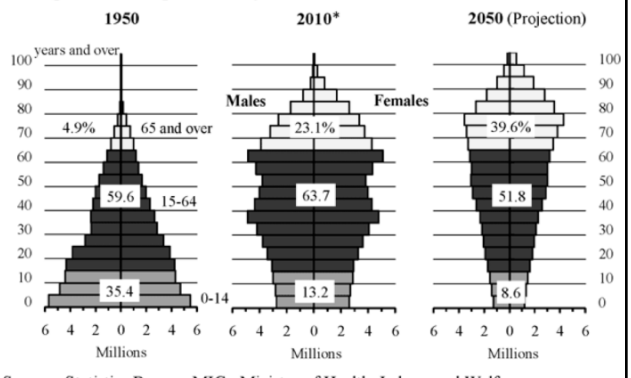
## Outline

- Background: Demographics and guiding theories of healthy aging
- Laboratory decision-making
- Real-world decision-making
- Structural and functional brain correlates
- Case studies: The seemingly high functioning older adult
- Pathological aging: Definitions, modifiable factors, and a little hope
- Denburg Lab current research

**Figure 2.3**
**Changes in the Population Pyramid**




Source: Statistics Bureau, MIC; Ministry of Health, Labour and Welfare.

## Guiding Theoretical Frameworks

## How the Brain Changes with Normal Aging

Age-Associated Memory Impairment

## How the Brain Changes with Normal Aging

Age-Associated Memory Impairment

Age-Associated Executive Impairment

(also known as the Frontal Lobe Hypothesis of Cognitive Aging)

## Somatic Marker Hypothesis

**(Damasio, 1994)**

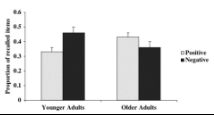
- Theory of how the brain and body impact decision making
- During decision-making, a person's emotions and feelings (from prior experiences) are key to making a decision
- Two brain areas are important to triggering various bodily changes (somatic states)
  - Ventromedial prefrontal cortex (VMPC)
  - Insular cortex
    - The somatic marker hypothesis predicts that damage to the VMPC sector and/or insular cortex will produce impairments (abolish or attenuate) in somatic responses to emotionally charged stimuli

## Socioemotional Selectivity Theory (SST) (Carstensen & colleagues)

SST is a motivational theory which suggests that secondary to an understanding of constraints on life longevity, older adults alter their strategies for emotional regulation.

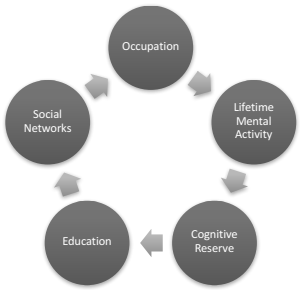
Older adults focus on and demonstrate a bias towards positively-valenced material.

Data from several cognitive domains supports this theory (memory, attention, decision making).



## Cognitive Reserve (CR)

- Multiple studies have identified Alzheimer's disease neuropathology in the brains of high-functioning individuals who have never exhibited cognitive problems.
- CR refers to the amount of damage that the brain can sustain before changes in cognition are evident.




## Older Adulthood is a Time of Critical, Complex, and Stressful Decision-Making

- Medical decision-making
- Financial decision-making
- Estate planning
- Change in roles/responsibilities following the death of a spouse/partner
- Change in residence/living arrangement

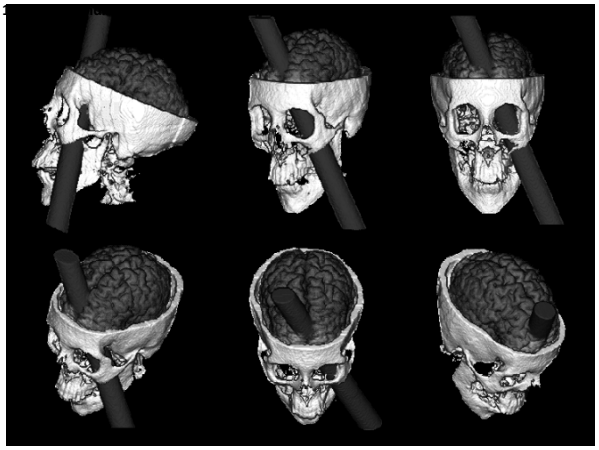
## The Problem

- Deceptive and fraudulent advertisers, telemarketers, and door-to-door salespeople are notorious for targeting older adults.
- Financial abuse of elders aged 65 years and older has risen from 8% in 1950 to an astounding 20% in 2010 (Infogroup/ORC, 2010).
- These statistics are likely underestimates, with only one in 25 cases being reported (Wasik, 2000).

## Why do some elderly make poor real world decisions and fall prey to fraud?

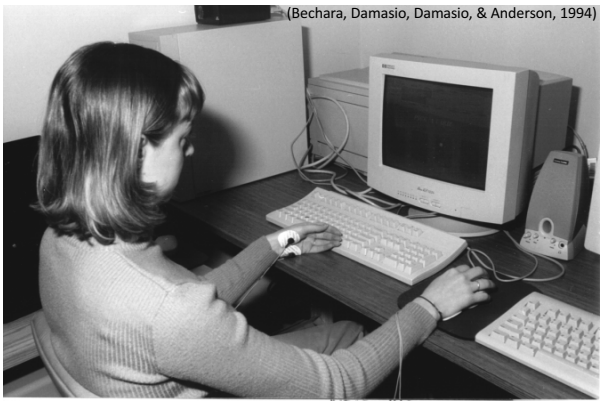
- Many possibilities have been raised
  - e.g., loneliness, gullibility, dementia
  - Largely anecdotal, few empirical data
  - Often do not accurately characterize victims
- We propose that cognitive vulnerability (though not a bona fide dementia), specifically related to flawed emotional responses that stem from abnormalities that develop in the brain's prefrontal cortex, may help explain why older adults are frequently victims of elder fraud.

## Laboratory Decision-Making

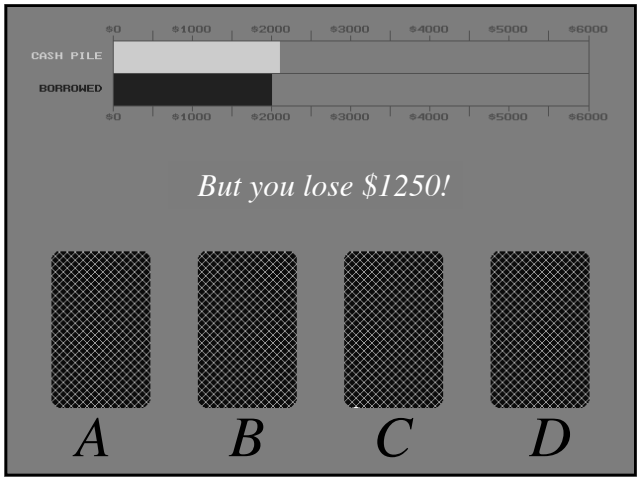


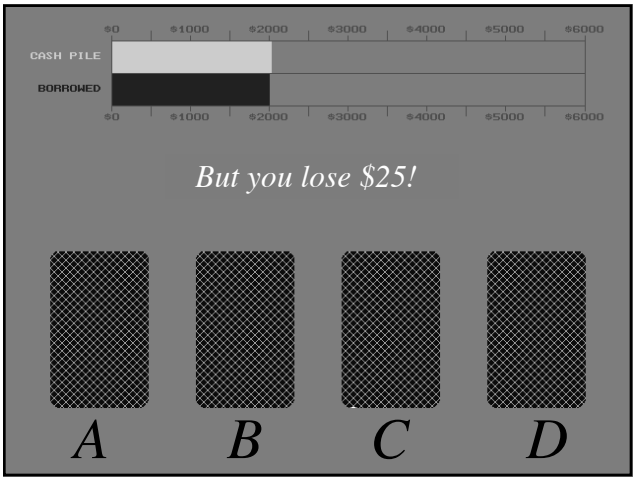
## Development of the Iowa Gambling Task (Bechara)

- Real-life difficulties in decision-making have been extremely difficult to capture in the laboratory.
- Well-known tasks of executive functioning have been found to be insensitive and non-specific.
- In sum, measurement of such deficits has been elusive.



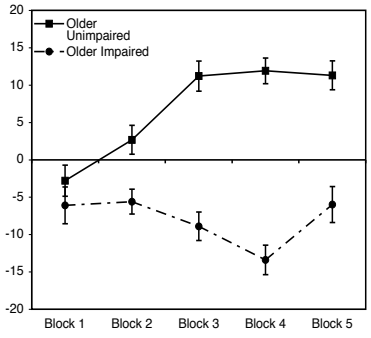
(Bechara, Damasio, Damasio, & Anderson, 1994)




## The Iowa Gambling Task

**(Denburg, Tranel, & Bechara, 2005)**

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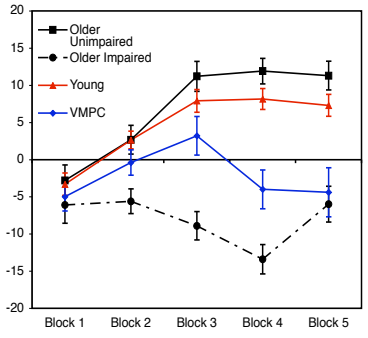
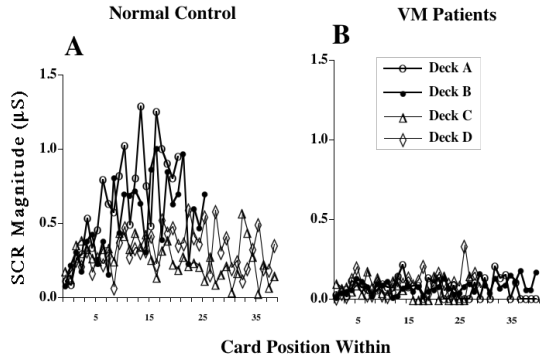


Demographic and cognitive characteristics of older participants

| Characteristic[a] | Statistic[b] | Participant group | | $p^c$ | Effect size[d] (*d* statistic) | Confidence interval[e] (95% CI) | Correlation with CD–AB[a] in older participants |
|---|---|---|---|---|---|---|---|
| | | Older–Unimpaired | Older–Impaired | | | | |
| Age | M | 70.3 | 71.1 | ns | .10 | −.63 to .82 | .07 |
| | S.D. | 8.3 | 8.0 | | | | |
| Education | M | 15.6 | 14.2 | ns | −.58 | −1.31 to .17 | .21 |
| | S.D. | 1.8 | 2.9 | | | | |
| Gender | % Females | 40 | 50 | – | – | – | – |
| Handedness | % RH | 93 | 100 | – | – | – | – |
| Health status | M | 1.60 | 1.64 | ns | −.06 | −.67 to .79 | .09 |
| | S.D. | 0.6 | 0.7 | | | | |
| Riskiness | M | 0.6 | 0.7 | ns | −.15 | −.70 to .98 | −.06 |
| | S.D. | 0.8 | 0.5 | | | | |
| BDI | M | 4.9 | 4.9 | ns | −.00 | −.74 to .74 | −.18 |
| | S.D. | 4.2 | 3.8 | | | | |
| WAIS-III digit span | M | 16.0 | 17.3 | ns | −.29 | −.46 to 1.03 | −.08 |
| | S.D. | 4.6 | 4.3 | | | | |
| Benton faces | M | 22.4 | 21.9 | ns | −.20 | −.95 to .56 | .17 |
| | S.D. | 2.3 | 1.6 | | | | |
| WRAT-3 reading | M | 51.0 | 48.9 | ns | −.63 | −1.35 to .14 | .25 |
| | S.D. | 3.1 | 3.6 | | | | |
| AVLT 30 min delay | M | 10.6 | 9.3 | ns | −.46 | −1.20 to .30 | .12 |
| | S.D. | 2.7 | 2.9 | | | | |
| BVRT errors | M | 3.3 | 4.5 | ns | −.65 | −.15 to 1.40 | −.30 |
| | S.D. | 1.6 | 2.1 | | | | |
| Verbal fluency | M | 41.6 | 38.7 | ns | −.33 | −1.07 to .42 | .17 |
| | S.D. | 7.8 | 9.0 | | | | |
| Trail making test A | M | 33.1 | 34.9 | ns | −.21 | −.54 to .95 | −.01 |
| | S.D. | 10.4 | 12.6 | | | | |
| Trail making test B | M | 74.5 | 82.8 | ns | −.28 | −.47 to 1.02 | −.03 |
| | S.D. | 27.8 | 31.3 | | | | |
| WCST perseverative errors | M | 7.3 | 9.7 | ns | −.67 | −.20 to 1.48 | −.23 |
| | S.D. | 4.0 | 3.1 | | | | |
| WCST categories | M | 6.0 | 5.8 | ns | −.48 | −1.29 to .36 | .13 |
| | S.D. | 0.0 | 0.6 | | | | |

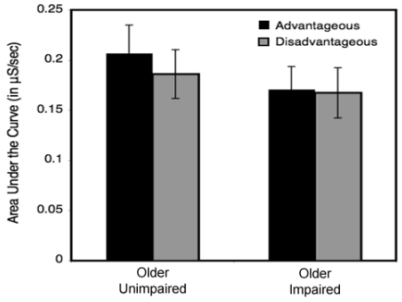
## Dependent Measure

- Skin conductance response (or SCR) as a proxy for somatic markers (i.e., emotion).
- Anticipatory SCRs: SCRs generated immediately prior to the point at which the subject turned a card from a given deck, i.e., during the time period the subject was pondering from which deck to choose




## Psychophysiological Studies

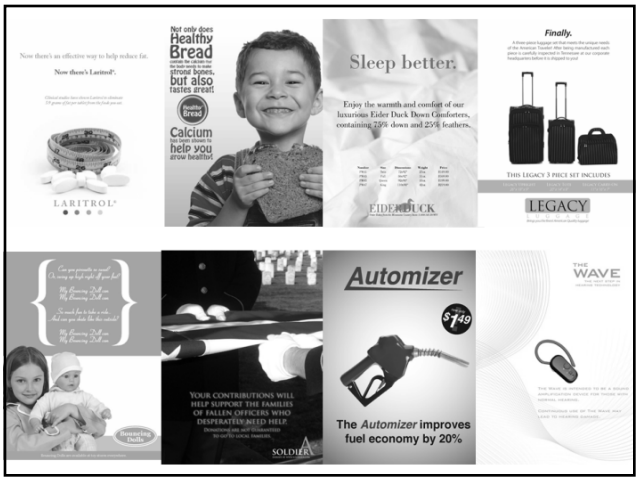
**(Denburg, Recknor, Bechara, & Tranel, 2006)**



## Real-World Decision-Making

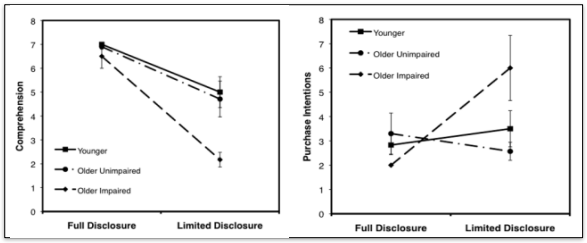
## Creation of Ad Stimuli

- Deceptive advertising claims were drawn from those cases rendered problematic by the Federal Trade Commission (FTC) during the last 10 years as published in their journal, *FTC Decisions*.
- For each FTC advertisement, non-deceptive counterparts were created.
- Deceptive and non-deceptive advertisements were admixed to create two advertising booklets.




## The Advertising Study

(Denburg, Cole, Hernandez, Yamada, Tranel, Bechara & Wallace, 2007)



# Financial Decision-Making

**(S. Shivapour, Nguyen, Cole, & Denburg, 2012)**

**Table 1 | Logistic Regression Models of FDMQ Scenarios to Age (i.e., Younger vs. Older).**

| Variable | Exp(b)* | 95% C.I. for exp(b) | | *Partial p*-value | *Overall p*-value |
|---|---|---|---|---|---|
| | | Lower | Upper | | |
| **PERSONAL FINANCE** | | | | | |
| Acquired knowledge | 1.694 | 1.234 | 2.298 | 0.001 | 0.000 |
| Rent allocation | 1.004 | 0.931 | 1.082 | 0.923 | |
| Credit card allocation | 1.095 | 1.005 | 1.194 | 0.038 | |
| Saving account allocation | 0.923 | 0.900 | 0.947 | 0.000 | |
| **IMPULSE PURCHASE** | | | | | |
| Acquired knowledge | 1.327 | 1.017 | 1.732 | 0.037 | 0.054 |
| Buy television | 0.617 | 0.300 | 1.268 | 0.189 | |
| **LOW PRECISION INVESTMENT** | | | | | |
| Acquired knowledge | 1.407 | 1.085 | 1.823 | 0.010 | 0.008 |
| Decision | 1.788 | 0.952 | 3.360 | 0.071 | |
| **FINANCIAL MANAGEMENT** | | | | | |
| Acquired knowledge | 1.333 | 0.966 | 1.840 | 0.080 | 0.000 |
| Savings account | 0.977 | 0.956 | 0.998 | 0.030 | |
| Certificate of deposit | 1.011 | 0.993 | 1.028 | 0.235 | |
| Business venture | 0.981 | 0.959 | 1.003 | 0.095 | |
| Credit card payment | 0.964 | 0.777 | 1.170 | 0.649 | |
| Spending | 0.968 | 0.917 | 1.022 | 0.240 | |
| Managed mutual fund | 1.008 | 0.990 | 1.027 | 0.364 | |
| Unmanaged mutual fund | 1.008 | 0.988 | 1.029 | 0.441 | |
| **FINANCIAL BEHAVIOR** | | | | | |
| Acquired knowledge | 1.515 | 1.150 | 1.996 | 0.003 | 0.000 |
| Promotion-oriented | 0.727 | 0.576 | 0.918 | 0.007 | |
| Prevention-oriented | 1.179 | 0.988 | 1.408 | 0.068 | |

*Exp(b) values are the exponentiated regression coefficient estimates.

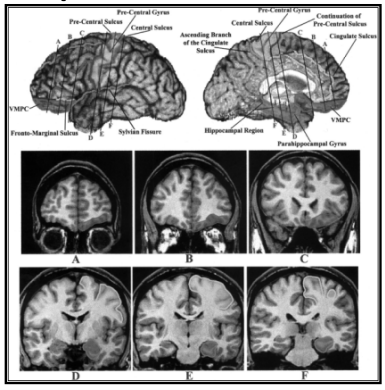
**Table 3 | Association of FDMQ Depth of Reasoning with Neuropsychological Performance.**

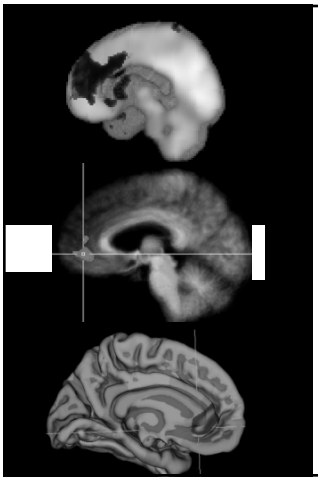
| Characteristics | Mean (SD) | Pearson *r* | Significance |
|---|---|---|---|
| **DEMOGRAPHICS** | | | |
| Age (years) | 73.62 (8.60) | −0.239* | 0.015 |
| Education (years) | 15.97 (2.72) | 0.211* | 0.032 |
| **PREMORBID AND CURRENT INTELLIGENCE** | | | |
| WRAT-3 Reading | 51.36 (4.00) | 0.128 | 0.205 |
| WASI Vocabulary | 66.65 (6.86) | 0.099 | 0.322 |
| WASI Similarities | 38.55 (4.26) | 0.089 | 0.400 |
| WASI Block Design | 36.61 (11.44) | 0.307** | 0.002 |
| WASI Matrix Reasoning | 23.07 (6.12) | 0.205* | 0.038 |
| **ATTENTION AND WORKING MEMORY** | | | |
| WAIS-III Digit Span | 17.17 (3.90) | 0.002 | 0.984 |
| WAIS-III Letter-Number | 10.11 (2.50) | 0.100 | 0.316 |
| **NUMERICAL SKILL** | | | |
| WAIS-III Arithmetic | 14.51 (3.36) | 0.127 | 0.204 |
| Numeracy | 6.25 (2.35) | 0.133 | 0.183 |
| **VISUAL SPATIAL** | | | |
| Benton Facial Recognition | 46.77 (4.19) | 0.115 | 0.255 |
| Rey-O Complex Figure Copy | 32.45 (2.82) | −0.060 | 0.662 |
| **LANGUAGE** | | | |
| COWAT | 44.17 (11.66) | 0.023 | 0.822 |
| Boston Naming Test | 18.75 (1.47) | 0.095 | 0.373 |
| **MEMORY** | | | |
| AVLT 30 min Delay | 9.90 (2.89) | 0.070 | 0.484 |
| Rey-O Complex Figure Delay | 16.26 (6.50) | 0.165 | 0.122 |
| RBRFT Errors | 4.36 (2.37) | 0.103 | 0.295 |
| **EXECUTIVE FUNCTIONING** | | | |
| WCST Perseverative Errors | 11.58 (9.70) | −0.237* | 0.020 |
| Trail Making B | 78.94 (29.32) | −0.216* | 0.030 |
| Iowa Gambling Task | 12.14 (38.01) | 0.205* | 0.041 |

*$p < 0.05$; **$p < 0.01$.

# Structural and Functional Neuroimaging Correlates of Disadvantageous Decision-Making

# What is happening to the brains of our "Impaired" older adults?



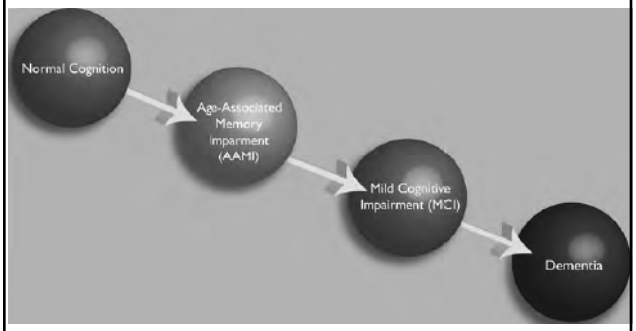



**Denburg & Harshman, 2010**
**Koestner, Hedgcock, & Denburg, 2016**

- FDG-PET (metabolism):
  - Decision Making
    - VMPC
      - Anterior cingulate (B)
    - DMPC
      - Frontal superior medial (R)
      - Frontal medial cortex (L)
  - Emotional States
    - Insula (R)
  - Executive Functioning
    - Inferior frontal gyrus (B)
    - Caudate (R)
- fMRI (brain activity during a task):
  - Decision Making
    - VMPC
- sMRI (cortical thickness):
  - Decision Making
    - VMPC
      - Rostral anterior cingulate (L)

**CASE STUDIES:**
**THE SEEMINGLY HIGH FUNCTIONING OLDER ADULT**

## The Aging-Dementia Cascade




## Causes of Dementia

- Degenerative disease
  - e.g., Alzheimer's, Lewy Body, Lobar dementias
    - Are the most important clinical category
- Focal/Multi-focal brain damage
  - e.g., stroke, tumor
- Medical or psychiatric illness
  - e.g., NPH, medications, alcohol/drugs, depression
    - Often reversible if caught early

***Can have a synergistic effect***

## Many *Modifiable* Risk Factors

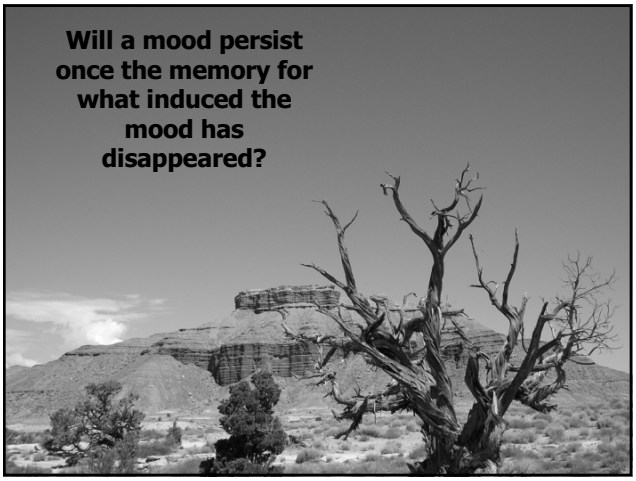
- Vascular risk factors and risk of AD
  - Washington Heights-Inwood Columbia Aging Project (WHICAP)
  - *N* = 1138, mean age 76.2, random sampling Medicare pts followed ~5.5 years, 272 developed dementia
    - Diabetes mellitus
    - Hypertension
    - Heart Disease
    - Elevated LDL Cholesterol
    - Smoking
    - High BMI

Luchsinger et al., 2005, *Neurology*

## Risk of Developing *Alzheimer's Disease*

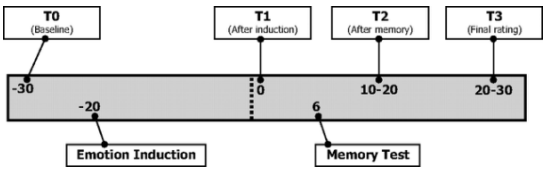
- Increased 1.7 fold when any ONE was present
  - Diabetes mellitus, hypertension, heart disease, smoking
- Increased 2.5 fold when any TWO were present
- Increased 3.4 fold when THREE were present
- Type II diabetes increased the risk to a greater extent than the other factors, followed by smoking.

Luchsinger et al., 2005, *Neurology*




## Timeline of the Experiment

**(2 inductions: Positive/Amusement and Negative/Sadness)**




Feinstein J S et al. PNAS 2010;107:7674-7679

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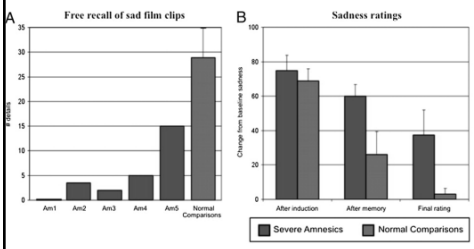
## Recollection of film clips and postfilm emotion ratings following the sadness induction




Feinstein J S et al. PNAS 2010;107:7674-7679

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# Current Decision-Making Work

**(funded by NIA/NIH)**

**The objective of this application is to characterize the neurobehavioral phenotypes of older persons who are at differing levels of risk for poor decision-making under stress.**

*Does a bout of acute stress change decision making patterns in healthy older adults?*

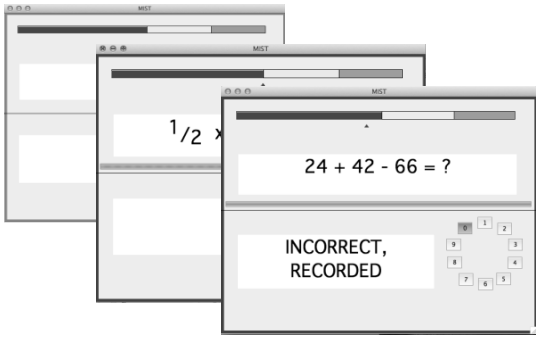
Or more colloquially:
*What happens to decision making when you put older adults into a brain scanner and stress them out?*

## How do you induce stress in the laboratory?

Trier Social Stress Test (TSST; Kirschbaum, Pirke, & Hellhammer, 1993)

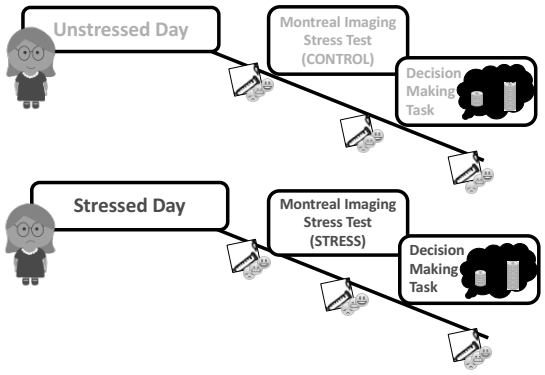
Montreal Imaging Stress Test (MIST; Pruessner et al., 2008)

# Montreal Imaging Stress Test




**Audio from Stress MIST day**

## Experimental Design

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- Previous Graduate/Medical Students: Georgina Moreno (NSF), Kameko Halfmann, Christopher Nguyen, Bryan Koestner, Sara Shivapour, Lyndsay Harshman, Erik Asp
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  - Dana Foundation Program in Brain and Immuno-Imaging
  - Takeda Pharmaceuticals
  - UI Internal Funding